Research Article

Computer Designing For New Compounds Starting From Anti-Hyperglycemic Thiazolidinedione Molecule

Mohamad Yahia Shikh Awad*
Department of Quality Control and Pharmaceutical Chemistry, Faculty of pharmacy, Aleppo University, Aleppo, Syria.
***Corresponding author's E-mail:** dr.awad88@hotmail.com

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ABSTRACT

In the quest for novel PPAR-γ agonists as putative drugs for the treatment of type 2 diabetes, a new test set molecules were proposed as bioisosteric analogues to the anti-diabetic thiazolidine-2, 5-diones (TZDs). Virtual screening compare fitting study of these new molecules with the generated discovery studio (DS) common feature PPAR-γ agonist's hypothesis, predicted that most of these are active as PPAR-γ agonist and hence they are as antidiabetic-type2 agents. Furthermore, molecular docking virtual screening for these active compounds, with the binding site of the PPAR-γ enzyme, revealed that the 2-pyrazolin-5-one and pyrazolidine-3,5-dione derivatives have higher or similar docking scores like that of the rosiglitazone. Also, the same docking study revealed that these compounds have the same binding site. This predicted that the designed proposed new molecules are considered PPAR-γ agonists active, and hence they are recommended to be synthesized as potential anti-diabetic type-2 agents.

Keywords: PPAR-γ agonists, 2-pyrazolin-5-one, pyrazolidine-3, 5-dione, Imidazolidine 2,4 dione, virtual screening molecular design.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease in which a person has high blood glucose, either because the body does not produce enough insulin, or because cells do not respond to the produced insulin.[1] The ancient Indians tested for diabetes by observing whether ants were attracted to a person's urine, and called the ailment "sweet urine disease" (Madhumeha).[2] In 1675 Thomas Willis added mellitus to the term, although it is commonly referred to simply as diabetes. Mel in Latin means honey; the urine and blood of people with diabetes has excess glucose, and glucose is sweet like honey. Diabetes mellitus could literally mean "siphoning off sweet water".[3]

Diabetes mellitus is mainly classified into two major types: type I and type II. The principle of classification depend on insulin.

- Type 1 diabetes: results from the body's failure to produce insulin.[2] Type 1 diabetes is an autoimmune disease, beta cells of Langerhans islets is completely destroyed, so people with Diabetes Type 1 are unable to produce insulin.
- Type 2 diabetes is referred to insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. Formerly referred to as non-insulin-dependent diabetes mellitus, (NIDDM) or adult-onset diabetes.[2] A person with diabetes type II either: Does not produce enough insulin. Or suffers from 'insulin resistance'. This means that the insulin is not working properly. There are many risk factors for type II Diabetes including age, family factor, body weight, cardiovascular problems and stroke, impaired fasting glycaemia , impaired glucose tolerance , several mental health problems.[4]
- Other types of diabetes mellitus is Gestational diabetes, when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. It may precede development of type 2 diabetes mellitus.[2] Congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes.[2] Latent autoimmune diabetes (LADA) of adults is a condition in which Type 1 diabetes develops in adults. Adults with LADA are frequently initially misdiagnosed as having Type 2 diabetes, based on age rather than etiology.[4]

Peroxisome Proliferator-Activated Receptor- γ (PPAR-γ) in diabetes and metabolism

The PPAR-γ receptors, which are abundant in adipocytes and are also present (to a lesser extent) in myocytes and other tissues, stimulate the expression of a number of genes that encode proteins involved in the metabolism of glucose and lipids. Their main biological effects in adipose tissue are promoting the differentiation of pre-adipocytes into adipocytes and increase the uptake of fatty acids and lipogenesis.

Antidiabetic activity through activation of Peroxisome Proliferator-Activated Receptor- γ (PPAR-γ)

There are many researches in the literature that could apply the activation of Peroxisome Proliferator-Activated Receptor- γ (PPAR-γ) in decreasing blood glucose level and treating diabetes mellitus type 2. The reported molecules that could activate PPAR -γ receptor and treat type 2 were

the Thiazolidinedione molecules (As it could discussed later).

Management of Diabetes Mellitus

Diabetes mellitus is a chronic disease which cannot be cured except in very specific situations. Management concentrates on keeping blood glucose levels as close to normal ("euglycemia") as possible, without causing hypoglycemia. This can usually be accomplished with diet, exercise, and use of appropriate medications (insulin in the case of type 1 diabetes, oral medications as well as possibly insulin in type 2 diabetes). Patient education, understanding, and participation is vital since the complications of diabetes are far less common and less severe in people who have well-managed blood glucose levels.[5 6]

The goal of treatment is an HbA1C level of 6.5%, but should not be lower than that, and may be set higher.[7] Attention is also paid to other health problems that may accelerate the deleterious effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise.[8]

Insulin is the drug of choice in type I Diabetes Mellitus treatment. Diabetes Mellitus type II treatment is mainly depends on oral hypoglycemic drugs which includes Sulfonylurea, α-Glucosidase inhibitors, Bisguanides, Thiazolidinedione, Metaglinides.

PPAR gamma agonists as Antidiabetic Type 2 Agents

The effect of thiazodinediones (TZDs) as antidiabetic agents is through amplifying post receptor events in the insulin signaling cascade.

Lehman et al[9] find that these post receptor events are largely mediated by ability of these agents to activate the Gama-peroxisome proliferators activated receptor (PPAR-γ)[10]. Binding of an agonist to this receptor, would alter its conformation, resulting in creating a binding cleft and recruitment of transcriptional co-activators.[11] After heterodimerization with another nuclear receptor, the PPAR-γ regulate target gene expression by binding to specific consensus DNA sequences, termed peroxisome proliferator responsive element (PPRE),[12] which are located in the regulatory regions of the target gene,[13] and result in an increase in gene transcription. This would be accompanied with regulation of lipid and glucose metabolism. The PPAR-γ receptor is predominantly expressed in adipose tissue and plays a pivotal role in adipocyte differentiation through regulation of genes involved in the differentiation of pre-adipocytes to adipocytes, suggesting that the PPAR-γ is an important component in the adipogenic signaling cascade and in lipid storage and utilization.[14] [15] Therefore, PPAR-γ is the principle molecular target in the development of insulin sensitizing antidiabetic agents.[16] New thiazolidinedione analogues, Rosiglitazone (Avandia)®(II),[17] troglitazone (Rezulin)® (III),[18] pioglitazone (ACTOS)®(IV),[19] have been approved by FDA and are currently marketed agents for the treatment of type 2 diabetes.

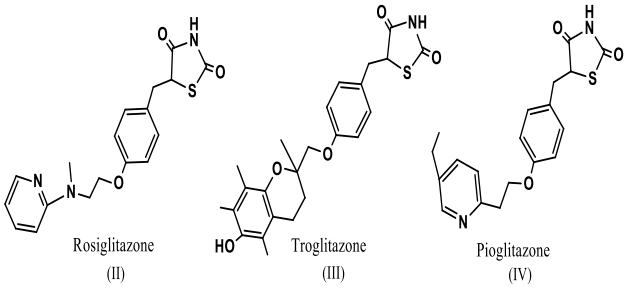


Figure 1: PPAR-γ agonist leads

The X-ray 3D structure of the PPAR-γ receptor has been reported in protein data bank website, in a complex with rosiglitazone ligand (II), where the ligand showed U-shaped conformation inside the receptor binding site cavity. The TZD head group appears to be oriented towards the left-most part of the cavity and forms three critical hydrogen bonding with three amino acids namely; His449, Tyr473, His323.[20] The other features extended through the U shape cavity exhibit Wan Der Waal interactions without any steric clashes. Such 3D crystal structure emphasized the settled SAR of Kulkarni et al,[21] in being consists of three pharmacophoric features; the acidic head feature that forms the above mentioned hydrogen bonding, the central aromatic region and the terminal lipophilic side chain through linkers that fit the complementary lipophilic U shaped binding cavity (Fig. 2a, b).

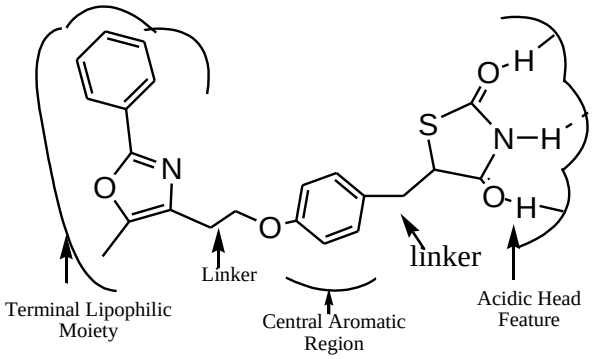


Figure 2a: 2D Representation of SAR of PPAR-γ agonists represented by compound (VI)

Figure 2b: 3D Representation of bio-active conformation of a lead PPAR-γ agonists rosiglitazone (II)

Literature survey revealed that; firstly, the thiazolidinedione ring could be replaced by closely related five-membered heterocyclic nuclei or even by an open chain moiety having the same features. For examples; oxazolidine-2,4-dione(X),[22] 1-oxa-2,4-diazolidine-3,5-dione (XI)[23] tetrazole(XII),[24] oxathiadiazole[25] , oxime[26] and α-alkoxycarboxylic acid derivatives (SB213068)(XIII),[27] arylaminoacids (farglitazone) (XIV),[28] and malonic acid derivatives (XV).[29] Secondly, such head group fragment could be attached to a central phenyl fragment by one carbon atom spacer with sp2 or sp3 hybridization state. Chirality at the attachment position at the head fragment showed that both isomers were active. Meanwhile, the central phenyl fragment could also be replaced by other flat aromatic rings like thiophene,[30] naphthalene,[31] benzofuran,[26] and benzoxazole.[32] Thirdly, the central flat aromatic moiety should be connected to the terminal lipophilic portion with 2 or 3 atoms` spacer. Fourthly, the lipophilic fragment could be comprised of 2-pyridyl[19], phenyl[35], branched cycloalky[36], benzoxazolyl,[33] oxazolyl[34], biphenyl[35] phthalozinone and benzoxazinone (XVI),[36] quercetin (XVII),[36] arylidenes (XVIII)[37] (Fig. 3).

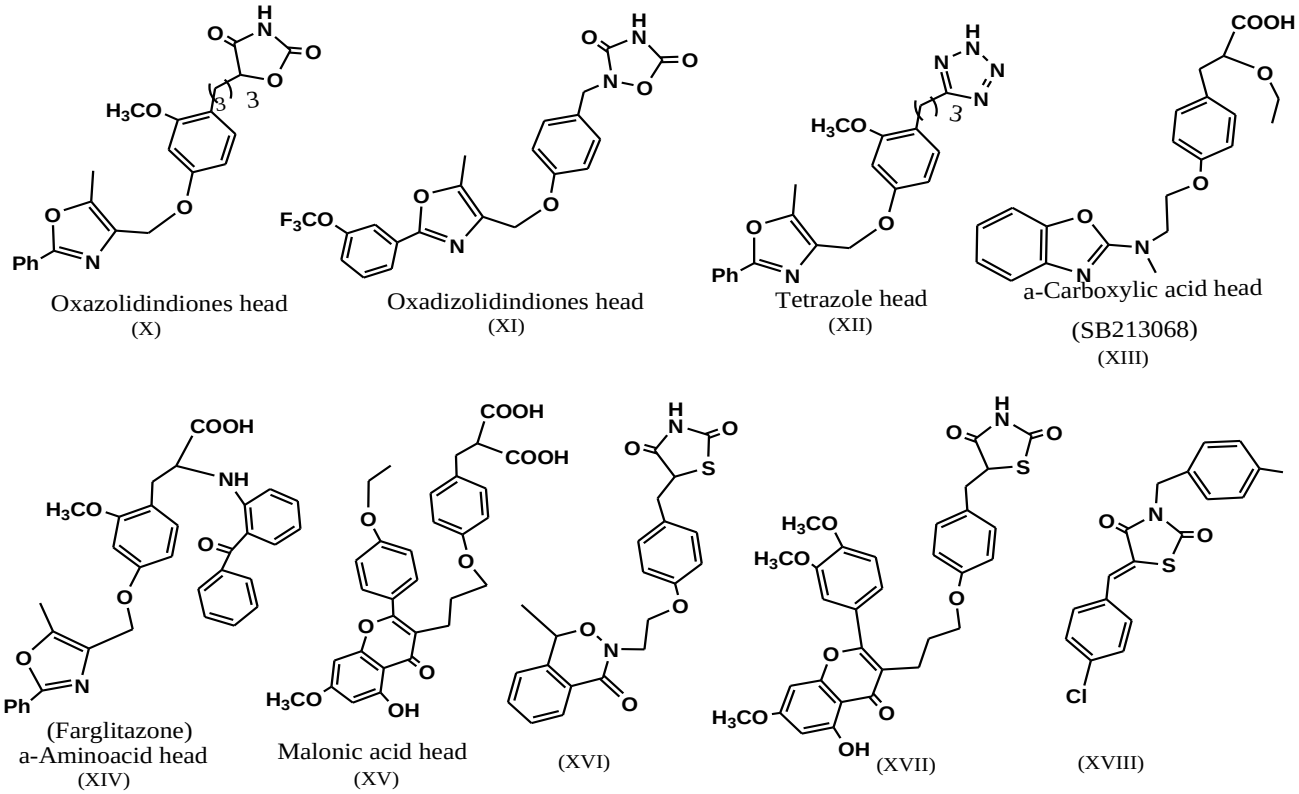


Figure 3: PPAR-γ agonists (cont.)

Aim of the study:

Current therapies to reduce plasma glucose levels have inherent problems including compliance, ineffectiveness. Accordingly, there is a need for more effective, orally administered agents, particularly ones that act as insulin sensitizing antidiabetic agents in peripheral tissue in order to normalize both glucose and insulin levels.[38]

Recently, a new series of 5-(4-alkoxybenzyl)-2, 4-thiozolidinediones (TZDs) were discovered as antihyperglycemic agents. The prototype agent Rosiglitazone® (I) lowered elevated glucose, plasma insulin and triglyceride levels in insulin resistant animals models, but showed no hypoglycemic effect in type I diabetic rats.

Therefore, we proposed, in this project, new structures derived from the lead Rosiglitazone® and we performed virtual fitting and docking studies of their structures with the PPAR-γ binding site or its hypothesis, using DS protocols.

MATERIALS AND METHODS

All molecular modeling processes and measurement of the results of the proposed compounds correlation were made using a computer modeling program (Accelrys Discovery Studio 2.5).

The formulations of the pharmaceutical compounds were drawn using two programs (ACDLabs), (ChemDraw).

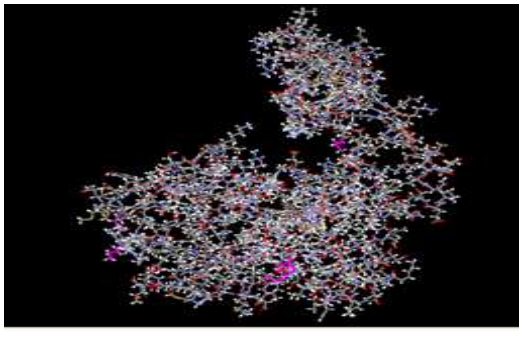


Figure 4: 3D structure of PPAR-γ enzyme (coded 3DZY) downloaded from www, pdb.org

The protein molecule in its 3D form was downloaded from the site Protein Bank (www.rcsb.org) (pdb) (Figure 4), the protein used with the name (PDB ID: 3DZY), molecular modeling and correlation energy were measured in comparison with the most powerful drug compound in this pharmacological group is rosiglitazone.

Configuring the Protein (Clean Protein) program Modeling (Accelerates Discovery Studio 2.5).

The Force field algorithm system was applied to the protein and all the proposed compounds where the algorithms were used as follows) Force field: CHARMm, Partial charge: MMFF94.

In order to minimize the protein energy and to ensure that it does not affect its three-dimensional shape, all the atoms except hydrogen are grouped together, fixed and bonded (Fixed atom constraint) and then the energy reduction protocol is performed (minimization).

In order to identify and configure the location of the drug link define sphere from selection (X: 3.641) (Y: 10.824) (Z: 25.239 (Radius 7.79244A) Figure 5.

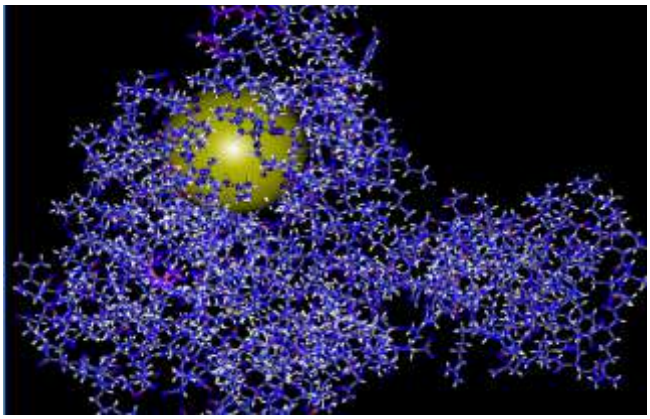


Figure 5: Binding site cavity (in yellow)

The drug rosiglitazone was formulated by Protocol (prepare ligands) and then draw the compounds (6 compounds).

The results of the correlation of the 6 developed compounds (CDOCKER energy) were measured based on the CDOCKER protocol - each compound alone, with rosiglitazone as a comparative compound in each measurement.

RESULTS AND DISCUSSION

The relationship between binding energy and modifications to the basic compound formula rosiglitazone was studied, Twenty-four compounds were designed but we will review the results of the six best compounds studied.

Compounds designed as stimulants for the PPAR receptor - can be considered for synthesis in laboratories as effective compounds for the treatment of diabetes type 2, Clinical tests are then performed to show the extent to which computer simulation results match clinical outcomes.

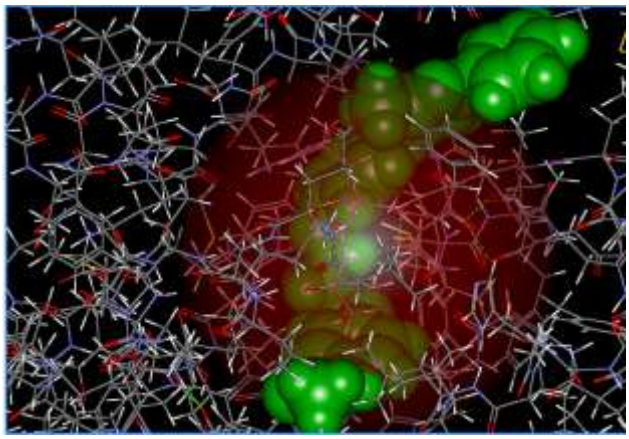


Figure 6: Docking of compound (YA1), the PPARγ Receptors

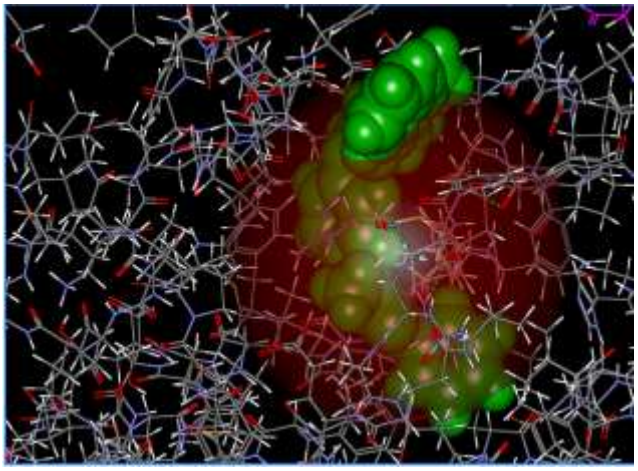


Figure 7: Docking of compound (YA2) the PPARγ receptors

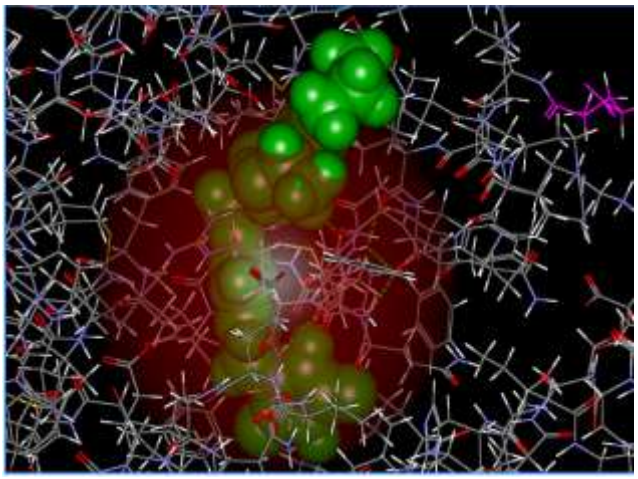
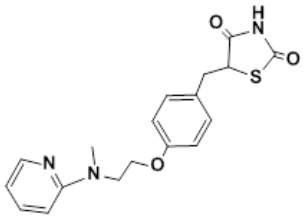
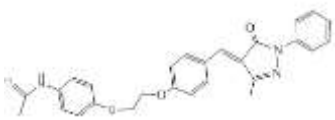
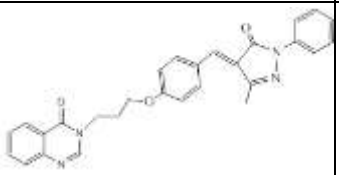
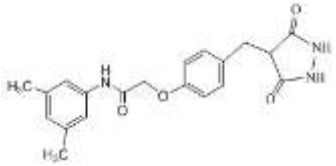
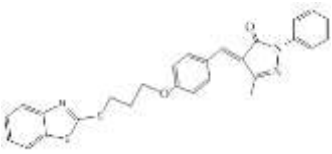
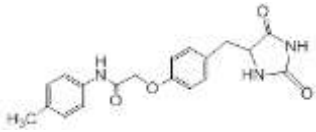
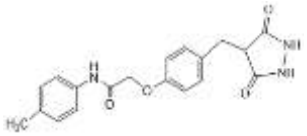


Figure 8: Docking of compound (YA3) the PPARγ receptors

The following table includes the results of the six best compounds developed on the computer:

Proposed designed compounds		CDocker score/ △ G(Kcal/mol)
Rosiglitazone		46.872
YA1		55.2983
YA2		51.7404
YA3		51.3858
YA4		49.0367
YA5		46.8344
YA6		46.7819

Modeling studies have found that the substitution of thiazolidinedione head with a 2-pyrazolidin-5-ones group gave the highest correlation values with the receiver as in (compound: YA1). Where the head of thiazolidinedione forms three hydrogen bonds as in the 2-pyrazoline-5-ones, the presence of the aromatic ring in compound YA1 gives additional binding to the compound rosiglitazone in the receptor cavity, and the fat side of YA1 is stronger in the receptor cavity than its rosiglitazone counterpart.

The head of the group Pyrazolidin, 3, 5 dion as-in (compound: YA3) gave lower correlation values than its 2-Pyrazolidin 5-ones (Compound: YA1).

The presence of two carbonyl groups on the pyrazoline ring as in YA3 reduces the binding values.

The presence of the benzothiazole 2-thiol group at the fatty end as in (compound: YA4) gives weaker correlation results than in the case of group 4-metoxy-phenyl (acetamide) (compound: YA1).

By comparing the compounds (YA2) and (YA4) we found that the group of 3-methylquinazolin-4-one in the lipophilic group gives better correlation results than if present Benzothiazole-2-thiol group.

It was also found that the presence of two methyl groups on the aromatic ring at the meta-sites at the fatty end (compound: YA3) yields better results than the presence of one methyl group in the Para site (compound: YA5).

The order of the nitrogen atoms in the pentagonal ring is important in terms of the results of the receptor binding values. For example, in the compound (YA5) containing the Pyrazolidin 3, 5-dion group gives better results than (Compound: YA6) containing the imidazolidin 2, 4 dione group.

Also, when increasing the number of atoms separating the central mass and the fatty end, it decreases the binding energy with the receiver (compound: YA4), where it contains five atoms and gave weak bonding energy compared to the rest of the compounds that maintained the separation distance of one or two atoms.

Through this study all the compounds shown except the compound (YA6) have higher binding energy than rosiglitazone, so they are able to stimulate the receptor PPAR- γ.

The compound (YA1) is the best compound in this study in terms of binding strength, so it is the strongest in this group to be the most effective drug and least in side effects.

CONCLUSION

This study concluded that compounds **(YA1, YA2, YA3 and YA4)** predicted to have high virtual screening scores through their fitting with the PPARγ agonist hypothesis and their docking with the real PPARγ binding site and thus, they can be considered as antidiabetic type 2 active hits. The structure of these active hits are presented in this project for further studies in the future.

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